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CONTRACT NUMBER: DAMD17-94-C-4081

TITLE: Fluorescence Optic Fiber Stereotactic Needle Ratiometer for Breast Tumor Diagnosis

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REPORT DATE: October 1996

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

# REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188



| 1. AGENCY USE ONLY (Leave blank) | 2. REPORT DATE | 3. REPORT TYPE AND DATES COVERED |
|---|---|---|
| | October 1996 | Annual ( 23 Sep 95 - 22 Sep 96) |

**4. TITLE AND SUBTITLE**
Fluorescence Optic Fiber Stereotactic Needle Ratiometer for Breast Tumor Diagnosis

**5. FUNDING NUMBERS**
DAMD17-94-C-4081

**6. AUTHOR(S)**
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**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

**10. SPONSORING / MONITORING AGENCY REPORT NUMBER**

**11. SUPPLEMENTARY NOTES**

**12a. DISTRIBUTION / AVAILABILITY STATEMENT**
Approved for Public Release; distribution unlimited

**12b. DISTRIBUTION CODE**

**13. ABSTRACT (Maximum 200 words)**

Activities during the second year were still restricted to gaining head start knowledge of the intended instrument from the development of a similar instrument for another project, an aerodigestive cancer diagnosis clinical study at Memorial Sloan-Kettering (MSK). An extension has been granted and a second extension will be requested based on advice from the reviewers at the recent site visit. Patient trials could not be started with just the approval from the Institutional Review Board (IRB) of Mass. Gen. Hosp., but require an Investigational Device Exemption (IDE) from FDA for this Phase I feasibility study. This was determined from the "Significant Risk" ruling by FDA shortly after the award of the Contract which also halted the the Phase II MSK study, both pending an IDE. The Sponsor has engaged the services of an experienced regulatory compliance consultant in drafting our IDE applications. Armed with recent favorable findings from our animal safety studies, the Phase II IDE application is soon to be filed followed by the Phase II application to permit the clinical trials for the device assembled under this contract. Ide approval is expected in 2Q97. In the interim, the device will be assembled, and the range finding data will begin to be collected in vitro on excised tissue. Preliminary baseline data already has been collected on breast tissue (fat, ductile, etc.) using related spectral fluorescence devices in order to develop the algorithim for data analysis. This work will be discussed.

| 14. SUBJECT TERMS | 15. NUMBER OF PAGES |
|---|---|
| Breast Cancer<br>Fluorescence, Fiber, Optic, Ratiometer, Needle, Biopsy, Tumor, Cancer | 11 |
| | 16. PRICE CODE |

| 17. SECURITY CLASSIFICATION OF REPORT | 18. SECURITY CLASSIFICATION OF THIS PAGE | 19. SECURITY CLASSIFICATION OF ABSTRACT | 20. LIMITATION OF ABSTRACT |
|---|---|---|---|
| Unclassified | Unclassified | Unclassified | Unlimited |

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10/31/96
Date

Table of Contents

## 5. Introduction

The Optic Fiber Stereotactic Needle-based Fluorescence Ratiometer for Breast Tumor Diagnosis (CD-Ratiometer) is an approach to improve the diagnosis of tissue, which is based on fluorescence spectroscopy. The goal of this project is to develop a CD-Ratiometer equipped with a small diameter optic fiber suitable for insertion into a hollow metallic needle for in vivo breast tumor diagnosis. A compact bread board CD-Ratiometer can measure the ratio of the fluorescence intensities at two pre-determined wavelengths, emitted from human tissue which has been photoexcited by a third pre-determined wavelength. This unit will be tested at Massachusetts General Hospital. The CD-Ratiometer can give information in real time concerning the condition of the tissue, information that normally is obtained from biopsy and pathology, thereby, possibly permitting the physician to make medical judgments more quickly. The device, through its needle-fiber optic probe, delivers an excitation light beam to a breast tumor, collects fluorescence emitted from the tumor and delivers this light back through a set of narrow band filters to a pair of photo-detectors for data analysis.

Researchers at the Mediphotonics Laboratory (MPL) at the City College of New York (CCNY) supported by Mediscience Technology Corp. (MTC) have been continuing to develop spectroscopic techniques to evaluate, diagnose and characterize tissues. Differences between malignant and normal or benign *in vitro* breast [1], gynecological [2] and colon [3] tissue samples were observed and ratios of their spectral intensities at various key wavelengths were determined.

During the report period, no work was performed on the Ratiometer under this contract because execution of the subcontract with City College of New York (CCNY) of CUNY was delayed until September 1st pending completion of the revisions of patient Consent Form required by the Human Use review and regulatory Affairs Division, USAMRMC, and resolution of indemnification issues raised by Research Foundation of CUNY. Contract extensions were obtained.

Recent research on breast tissues [4] demonstrated that the diagnostic accuracy would be improved using multiple wavelengths for tissue measurements as criteria to separate the normal and abnormal tissues. Therefore, an updated algorithm from these results [4] will be incorporated for tissue diagnostics using the Ratiometer unit (Fig.1).

**6. Body**

Regulatory Compliance Matters

Planned testing on human subjects for this contract had to be postponed due to a ruling by the FDA in January 1995 involving a similar Mediscience device for another clinical study but applicable also to this study. That target organ was the oral cavity. That ruling required the Company to conduct additional toxicology studies in an animal model before the FDA would consider granting an Investigation Device Exemption ("IDE") to conduct in-vivo clinical studies on humans. The ruling designated that fluorescence spectral device and, by inference, all such devices as "Significant Risk" as opposed to "Nonsignificant Risk".

The additional regulatory compliance burden placed on the Company by the FDA has necessitated the purchase of specialized regulatory affairs services by Mediscience for developing, drafting, and negotiating/defending the appropriateness of the required IDE application(s) with the FDA. During the second year of this contract, the toxicology study described above was completed. Data collected initially from human oral cavity study prior to the FDA ruling is currently in the process of its assemblage into the clinical study report as a part of a Phase II IDE resubmission on or about November 1, 1996.

Mediscience expects the "Breast Needle Ratiometer" to benefit from the favorable results of the toxicology study. The company expects to file for the "Breast Needle Ratiometer" Phase I IDE with the FDA by April 1, 1997, and prior to that time it expects to have completed the assembly of the "Breast Needle Ratiometer". This work has already begun. Also, final range finding studies with the needle probe will have begun from ex-vivo optical ratio analysis of freshly excised breast tumor tissue. Preliminary ex-vivo range finding studies, not using the needle probe, were already successfully concluded. Hence, the in-vivo human clinical feasibility study can begin immediately after the FDA approves the "Breast Needle Ratiometer" IDE.

Other regulatory driven activities begun that are related to this contract include the purchase of design engineering services to properly document the "Breast Needle Ratiometer" device with drawings, parts and assembly specifications and procedures to fulfill FDA Good Manufacturing Practice requirements. Additionally, the Company will now provide an on-site field service engineer to support its clinical studies and is further required by the FDA to provide for professional study monitoring and data management by an independent clinical research organization.

Summary of Activities

Because the subcontract with CCNY was delayed, the PI was reassigned to other projects. However, related research, not under the subcontract, continued at CCNY. A cancer diagnosis procedure [4] was developed as summarized by the flow chart, Fig.1. This is reflected in the design of the filter wheel and planned fabrication of the unit. Also, during this period, optic fiber and needle acquisitions were made and patient consent and subcontract issues were resolved

The work plan for the upcoming year is :

(1) Subcontract to CCNY to assemble a needle ratiometer unit
(2) Measurements on *in vitro* tissues including breast sample at CCNY and MGH.
(3) Testing *in vivo* tissues at MGH pending IDE approval (MTC)
(4) Final report

The plan for the next period is shown in the table II.

**7. Conclusion**

The project's parameters have expanded from the original plan owing to the IDE requirements. This motivated our request for the twelve month extension that was granted. However, that extension will carry the project into just the start of the human clinical feasibility trials. Therefore, a second twelve month extension was requested and granted to permit the completion and assessment of the clinical feasibility trials. Positive findings would provide the basis for expanded clinical trials and a Phase II IDE application to FDA. During this period, the algorithm for wavelength pairs will be refined for use in the needle ratiometer unit.

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Table I, Filter selection for Fiber Needle-based Fluorescence Ratiometer

| **For Fluorescence mode** | | |
|---|---|---|
| Excitation Wavelength | Fluorescence Wavelength | Fluorescence Wavelength |
| 300 nm | 340 nm | 440 nm |

| **For Synchronous mode** | |
|---|---|
| Excitation Wavelength Pair | Probe Wavelength Pair |
| 520/460 (nm) | 520/460 (nm) |
| Excitation Wavelength | Probe Wavelength |
| 420/460 (nm) | 420/460 (nm) |

Table II Project Schedule

| Tasks | Time Table (Months) 0 (Oct.) 1 Nov. 2 Dec. 3 Jan. 4 Feb. 5 Mar. 6 Apr. 7 May 8 Jun 9 July 10 Aug. 11 Sept. 12 |
|---|---|
| Order parts | 0----------0 |
| Optics<br>Electronics<br>Mechanics | |
| Software enhancement | 0----------0 |
| Unit assembly | 0----------0 |
| Enhance needle design | 0----------0 |
| Test unit operation | 0----------0 |
| Test in vitro tissues | 0----------0 |
| Hospital test in vitro | 0----------0 |
| IDE approval for in vivo test (?) | 0----------0 |
| Report | 0----------0 |

# Fig. 1 Flow Chart of Cancer detection Using Synchronous Scan and fluorescence